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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,491	03/19/2004	Mary Cismowski	60388-AB-PCT-US JPW/GJG/J	8086

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/804,491	CISMOWSKI ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-41 and 52-78* is/are pending in the application.

4a) Of the above claim(s) *52-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,32,34-41 and 72-78* is/are rejected.

7)☒ Claim(s) *31 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 19 March 2004 as a continuation of US patent application 09/709,103, which is a continuation of international application PCT/US99/10151 filed 7 May 1999, which claims benefit of US provisional applications 60/084,842 filed 8 May 1998 and 60/103,355 field 7 October 1998. The preliminary amendment filed 19 March 2004 has been entered. Claims 1-78 were filed. Claims 1-29 and 42-51 were canceled and claims 30, 32, 33, 62-65, 68-71, 74, 76 and 77 were amended in the 19 March preliminary amendment. Claims 30-41 and 52-78 are pending.

Election/Restrictions

Applicant's election with traverse of Group I (claims 30-41 and 72-78) in the reply filed on 17 December 2004 is acknowledged. The traversal is on the ground(s) that examination of the additional claims of Groups II and III along with the claims of Group I does not impose a serious burden. This is not found persuasive because, as stated in the restriction requirement, the Inventions of Groups I-III are separately classified, which is *prima facie* evidence of the additional burden imposed by searching the inventions together. Furthermore, as described in the restriction requirement, each Group is limited to comprising elements which are not required to practice the other methods as claimed. Therefore, a search of any one method does not adequately cover the scope of the other methods, and a determination that any one method is anticipated by the art does not render the other methods obvious without an additional search. Likewise, given the divergent subject matter embraced by the different Groups, a determination that any one Group is free of the art does not evidence patentability of the other Groups.

Therefore, examination of the distinct methods together in a single application would impose a serious burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 52-71 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the 17 December reply.

Claims 30-41 and 72-78 are presently under consideration.

Priority

It is noted that the priority claim added to the specification in the preliminary amendment filed 19 March 2004 does not include the current status of the 09/709,103 application, which is now US Patent No. 6,733,991. Applicant is requested to amend the specification to include the patent number in the priority claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 32, 34-41 and 72-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims are directed to a method for identifying a compound that modulates signal transduction in a cell comprising contacting a cell that expresses an AGS protein with a test compound and determining the effect of the test compound on the activity of the AGS protein. Upon reviewing the specification, the Examiner can find no explicitly limiting definition of an AGS protein. In the paragraph bridging pages 6-7, the specification states:

> [I]n one embodiment, the AGS molecules stimulate the activity of one or more G proteins involved in a G protein-mediated signal transduction pathway, e.g., a pheromone response cascade in yeast, to thereby activate G protein-mediated signal transduction independent of G protein coupled receptor stimulation.

Based on this, the AGS protein of the claims is construed to encompass a genus of expressible molecules that stimulate the activity of one or more G proteins independent of G protein coupled receptor stimulation. In addition, because the definition is provided as "one embodiment" of an AGS protein, the AGS protein of the claims is also construed as encompassing AGS proteins that are dependent on G protein coupled receptor stimulation (*e.g.*, G-protein coupled receptors).

The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). The Guidelines further state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

As the AGS protein of the claims is required for operability of the invention, it is clearly a critical element of the claims and, therefore, must be adequately described. Although AGS proteins having the structural and functional properties of G-protein coupled receptors are conventional in the art, expressible molecules that stimulate the activity of one or more G proteins independent of G protein coupled receptor stimulation were not conventional in the art at the time of filing. In fact, the art available prior to the effective filing date of the instant application does not disclose a single expressible AGS protein that is not a G protein coupled receptor.

Although the application provides a detailed description of a single receptor independent AGS protein (*i.e.*, the polypeptide comprising SEQ ID NO: 2) and in Example 6 identifies some residues that are critical to function of the AGS, this single species fails to adequately represent a genus that encompasses any expressible AGS,

independent of structure. This is clearly evidenced by the post-filing art, which teaches that the three receptor independent AGS proteins presently known are structurally and functionally distinct, each from the other. Cismowski *et al.* (2001) *Life Sci.* 68:2301-2308 teaches, "[a]lthough each AGS protein activates G-protein signaling, they do so by different mechanisms within the context of the G-protein activation/deactivation cycle" (abstract) and "AGS1, AGS2 and AGS3 do not share any apparent structural similarities that suggest common mechanisms of G-protein activation" (page 2304, second full paragraph). Thus, Cismowski *et al.* teaches that the genus of AGS proteins capable of receptor independent G protein activation is structurally and functionally diverse and clearly embraces molecules that were not described in the instant specification such that the skilled artisan would recognize that Applicant was in possession of the full scope of the genus at the time of filing.

Furthermore, given the functional diversity of AGS proteins which is now known to exist, the skilled artisan would not expect the single disclosed species of "a polypeptide capable of inhibiting the activity of the AGS protein" (*i.e.*, the polypeptide comprising SEQ ID NO: 25) to adequately describe the genus encompassed thereby. That is, the skilled artisan would not have viewed the disclosure of the polypeptide comprising SEQ ID NO: 25, which is capable of inhibiting the activity of the protein comprising SEQ ID NO: 2, as representative of a genus of polypeptides capable of inhibiting the activity of any AGS protein. Still further, the skilled artisan would not have viewed the single species as representative of all proteins having the ability to inhibit the activity of a polypeptide comprising SEQ ID NO: 2. Therefore, the skilled artisan would not have

viewed the disclosure as providing adequate descriptive support for any polypeptide capable of inhibiting the activity of an AGS protein other than the polypeptide comprising SEQ ID NO: 25.

Although the application discloses an assay with which one might identify proteins having the function of an AGS protein or a polypeptide capable of inhibiting the activity of an AGS protein, an adequate written description of a protein requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the protein itself. It is not sufficient to define protein solely by its principal biological property (*i.e.*, it is an AGS or inhibits the activity of an AGS protein) because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any protein with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming a method of using any proteins that achieves a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of expressible AGS proteins or proteins capable of inhibiting the activity of an AGS protein. Therefore, only the described receptor independent AGS protein comprising an amino acid sequence having at least 97% identity to SEQ ID NO: 2 and stimulating G protein

activity in a receptor-independent manner and the described polypeptide capable of inhibiting the activity of the AGS protein comprising SEQ ID NO: 25 meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 30, 32, 34-41 and 72-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method practiced with an AGS protein that is a G protein coupled receptor or a receptor independent AGS protein comprising an amino acid sequence having at least 97% identity to SEQ ID NO: 2 and a polypeptide capable of inhibiting the activity of the AGS protein comprising SEQ ID NO: 25, does not reasonably provide enablement for any AGS protein or any polypeptide capable of inhibiting the activity of an AGS protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: As discussed above, the claims are directed to a method of using an AGS protein, which AGS protein is construed to encompass a broad genus of any expressible molecules that has the functional property of stimulating the activity of one or more G proteins independent of G protein coupled receptor stimulation, and a method of using any polypeptide capable of inhibiting the activity of any AGS protein.

State of the prior art and level of predictability in the art: Although AGS proteins having the structure and function of G protein-coupled receptors are conventional in the art, he art teaches that the genus of AGS proteins capable of receptor independent G protein activation is structurally and functionally diverse and the specification fails to disclose the structural properties that define the broad genus of proteins having the recited function (see the discussion of Cismowski *et al.*, *supra*).

Amount of direction provided by the inventor and existence of working examples: The application provides a detailed description of a single receptor independent AGS protein (*i.e.*, the polypeptide comprising SEQ ID NO: 2) and in Example 6 identifies some residues that are critical to function of the AGS. Further, the specification discloses the structure of a single species of "a polypeptide capable of inhibiting the activity of the AGS protein" (*i.e.*, the polypeptide comprising SEQ ID NO: 25). However, as described above, the specification fails to convey the characteristics common to a genus that encompasses any expressible AGS such that the identifying characteristics of the genus would be readily apparent to the skilled artisan. Finally, the application discloses an assay with which one might identify proteins having the function of an AGS protein or a polypeptide capable of inhibiting the activity of an AGS protein.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, making the AGS protein and polypeptide capable of inhibiting AGS protein activity such that the method could be practiced commensurate with the full scope of the claims would require undue experimentation. The claims encompasses a method of using a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function has not been defined. The art teaches that the genus of AGS proteins capable of receptor independent G protein activation is structurally and functionally diverse and the specification fails to disclose the structural properties that define the broad genus of proteins having the recited function. In the absence of such a relationship either disclosed or in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this deficit since one would have no knowledge beforehand as to whether or not any given compound would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Thus, due to the art recognized unpredictability of the determinants that define a receptor independent AGS protein or a polypeptide capable of inhibiting the activity of any AGS protein and the lack of guidance in the specification or prior art with regard to how to make the molecules required to practice the method, it would require undue experimentation to practice the invention commensurate with the full scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 30 and 34-41 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Pausch *et al.* US Patent No. 5,691,188.

In Example 3, Pausch *et al.* discloses a method of identifying a compound that modulates signal transduction in a cell comprising providing a cell that expresses an AGS protein (*i.e.*, the G protein coupled somatostatin receptor), contacting the cell with a test compound, determining the effect of the test compound on the activity of the AGS protein and identifying the test compound as a modulator of signal transduction based on the ability of the compound to modulate the activity of the AGS protein (see especially column 15, lines 12-15 and 20-27). The method of Pausch *et al.* anticipates the instant claim 30.

Furthermore, in the method of Pausch *et al.*: the cell has been engineered to express the AGS protein according to claim 34 (see especially column 14, lines 47-52) and the cell is a yeast cell that has been engineered to express a G protein α subunit according to claim 35, which is a

mammalian chimeric G protein α subunit according to claim 36 comprising the amino terminal domain from GPA1 and the C-terminal sequence from rat Gαi2 according to claim 37 (see especially column 14, lines 55-58). Still further, the yeast cell of Pausch *et al.* has been engineered such that the activity of the AGS protein is monitored by measuring the activity of the yeast signal transduction pathway according to claim 38 (see especially column 15, lines 3-8). Pausch *et al.* teaches that the assay disclosed therein provides a measure of agonist binding to the AGS protein according to claim 39, which results in activation of the yeast pheromone pathway as a consequence of interaction of the AGS protein with a target G protein according to claims 40 and 41(see especially column 15, lines 11-14).

Thus, the method of Pausch *et al.* comprises each of the limitations of claims 30 and 34-41 and the claims are properly rejected as anticipated thereby.

Claims 30, 32 and 34 rejected under 35 U.S.C. 102(b) as being anticipated by Allen *et al.* US Patent No. 5,573,908.

Allen *et al.* discloses a method of identifying a compound that modulates signal transduction in a cell comprising providing a cell that expresses an AGS protein (*i.e.*, a constitutively active α_1-adrenergic receptor), contacting the cell with a test compound, determining the effect of the test compound on the activity of the AGS protein and identifying the test compound as a modulator of signal transduction based on the ability of the compound to modulate the activity of the AGS protein (see especially claim 3). The method of Allen *et al.* anticipates the instant claim 30.

Furthermore, in column 3, line 35, Allen *et al.* teaches that the receptor used in the method can be isolated from human cells according to claim 32 and the cell is engineered to express the AGS protein by introducing a vector which encodes the AGS protein according to claim 34 (see especially claim 1).

Thus, the method of Allen *et al.* comprises each of the limitations of claims 30, 32 and 34and the claims are properly rejected as anticipated thereby.

Allowable Subject Matter

Claims 31 and 33 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636